PN - CN1186666 A 19980708

PD - 1998-07-08

PR - CN19970119871 19971229

OPD - 1997-12-29

TI - Azithromycin suppository and ointment

AB - As locally applied medicine, Azithromycin suppository consists of Azithromycin 5-50 wt% and suppository matrix 50-95 wt%, and Azithromycin ointment of Azithromycin 0.5-20 wt% and ointment matrix 80-99.5 wt%. Owing to the wide autiseptic spectrum and strong antiseptic capacity, the said suppository and ointment can produce medicinal effect directly without irritation to gastrointestinal tract, biochemical reaction in liver and toxic side effect to liver. The present invention is effective medicine for curing various VTD's.

IN - CHANG JIANG (CN);SHEN YONGHONG (CN);WANG LIANHUA (CN)

PA - JINZHOU CITY PHARMACEUTICAL FA (CN)

IC - A61K31/70 ; A61K9/06 ; A61K9/02

TI - Locally applied medicine, useful in the treatment of VTD's, comprises azithromycin and either suppository matrix or ointment matrix

PR - CN19970119871 19971229

PN - CN1186666 A 19980708 DW200337 A61K31/70 000pp

PA - (JINZ-N) JINZHOU CITY PHARM FACTORY NO

IC - A61K9/02 ;A61K9/06 ;A61K31/70

IN - CHANG J; SHEN Y; WANG L

AB - CN1186666 NOVELTY - Locally applied medicine, comprises either:

- (1) azithromycin (5-50 weight% (wt.%)) and suppository matrix (50-95 wt.%); or
- (2) azithromycin (0.5-20 wt.%) and ointment matrix (80-99. 5 wt.%).
- USE - The medicine is used for curing various VTD's.
- ADVANTAGE - Owing to the wide antiseptic spectrum and capacity, the medicine can produce medicinal effect without irritation to gastrointestinal tract or biochemical reactions or toxic side effects to the liver.
- (Dwg.0/0)

OPD - 1997-12-29

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Claims: 1 Page, Specification: 6 Pages (Attached). Pictures: 0 Page

[54] Title of Invention Azithromycin Effervescent Tablet for the Vagina

[57] Abstract

The invention relates to an azithromycin effervescent tablet for the vagina that is specially designed for gynecological diseases. The effective component is azithromycin, which is 250.0 grams per 1000 tablets when the drug is anhydrous. The dosage form ingredients include 200.0g tartaric acid, 150.0g sodium bicarbonate, 400.0g starch, 200.0g cellulose microcrystalline, 12.0g talc powder. Or the formula may include 500g azithromycin and proportionally reduced ingredients. The vaginal effervescent tablet containing 250mg or 500mg per tablet is prepared according to the formula and routine preparation process. This invention boasts a reasonable formula and preparation process. With good stability and notable curative effects, the product is particularly suitable for women with cervicitis, vaginitis, gonorrhoea, and complex infections.

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Claims

1. An azithromycin vaginal effervescent tablet is characterised by effective components and dosage form ingredients according to formula (1), which is calculated based on 1000 tablets:

Azithromycin (calculated according to anhydrous azithromycin)	250.0g
Tartaric acid	200.0g
Sodium bicarbonate	150.0g
Starch	400.0g
Cellulose microcrystalline	200.0g
Talc powder	12.0g

Or according to formula (2), which is calculated based on 1000 tablets:

Azithromycin (calculated according to anhydrous azithromycin)	500.0g
Tartaric acid	148.0g
Sodium bicarbonate	111.0g
Starch	296.0g
Cellulose microcrystalline	148.0g
Talc powder	9.0g

Alcohol is added as an adhesive during preparation according to formula (1) or (2). A vaginal effervescent tablet containing 250mg or 500mg azithromycin is prepared according to the routine preparation process for effervescent tablets.

2. According to Claim 1, the azithromycin effervescent tablet comprises 500ml of 95% alcohol.

Specification

Azithromycin Vaginal Effervescent Tablet

The invention relates to azithromycin, a new macrolides antibiotic that is a chemical drug. It refers specifically to azithromycin vaginal effervescent tablets.

Azithromycin (chemical name: 9-deoxy-9α-aza-methyl-9α-erythromycin A; English Name: azithromycin) is a 15-ring macrolides antibiotic developed by SOOR PLIVA in Croatia. Since its entry into the market in 1988, the drug has quickly become popular worldwide with a broad antibiotic spectrum, acid stability, long-term effect and high bioavailability.

According to the references, azithromycin is not only used in acute pharyngitis, amydalitis, acute tympanitis, acute nasosinusitis, acute bronchitis, acute attacks of chronic bronchitis, atypical pneumonia, bacterial pneumonia, but also in inflammation of reproductive systems like gonorrhoea, non-gonorrhoea urethritis, trachoma chlamydozoan infection, and complex infections of gonococci and chlamydozoan. In recent years, acute gonorrhoea has become the most common sexually transmitted disease in China. Nearly 30% of gonorrhoea patients have trachoma chlamydozoan infection of the urinary and genital system. Azithromycin is effective for both pathogens, and has been listed as the first choice for these kinds of diseases in clinical practice.

At present, although raw drugs, capsules, suspension, and water injection of azithromycin have been produced and used in clinical practice, there is no report available on azithromycin vaginal effervescent tablets at home and aboard. Generally speaking, oral drugs should be absorbed into the blood via the gastrointestinal tract, and then distributed in the whole body through blood circulation, thus effective gradients are greatly reduced at the sites of infection. One report related that when administered orally, only 37% of azithromycin tablets or capsules is absorbed via the gastrointestinal tract, while the others are secreted in vitro, which will cause great loss. (Foulds G, et al: The Pharmacokinetics of azithromycin in human serum and tissues. Journal of Antimicrobial Chemotherapy. 1990, 25 (Suppl A.): 73-82). In the form of water injection, the drug can directly enter the blood circulation without gastrointestinal absorption. Although blood concentration is high, effective drugs can barely enter the sites of infection to play their due role, especially in the case of gynecologic inflammation. Besides, many people suffer from gastrointestinal diseases. Azithromycin is a strong stimulus to the gastrointestinal tract, and thus causes much discomfort. Oral or injection drugs will also place a greater burden on the liver and kidneys.

Azithromycin in the present dosage form can therefore hardly be effected as predicted, despite the fact that the drug itself has good curative effects in gynecological inflammation or contagious diseases. Therefore, it leaves a void in the present techniques.

The invention aims to use azithromycin, the new broad-spectrum antibiotics that are specially designed for gynecological diseases, at localized sites in the form of a vaginal effervescent tablet, so that the drug will exert maximum curative effects. The product is suitable for various inflammatory or sexually transmitted diseases in gynecology.

In consideration of the fact that azithromycin comprises 2 crystal H_2O, and the friability of the tablet is likely to be high, the inventor adds more ingredients to the product. Based on the related requirements for vaginal effervescent tablets in Chinese pharmacopoeia, the PH value of its water solution should be slightly acidic, and gas can be emitted at a suitable volume. Conditions are selected regarding fluidity, compressibility, and foam according to the physical and chemical properties of the main gradient. After much research and tests, and selection of various formulae, two formulae are finally selected with hygroscopic starch and microcrystalline cellulose as the filling agent, talc powder as the flow aid and anti-tackiness agent, tartaric acid and sodium bicarbonate as an effervescent agent. The prescriptions are simple, reasonable, and steady, which are suitable for industrial production and meet the requirements of the preparation process and properties of the final products. Several major descriptions are listed in Table 1 (calculated according to the volume of 1000 tablets).

Table 1

Serial Number / Raw Materials And ingredients	1	2	3 (this invention)	4 (this invention)	5	6	7
Azithromycin	250	250	250	500	250	250	250
Citric Acid	200	---	---	---	---	---	---
Boric acid	---	200	---	---	---	---	---
Tartaric acid	---	---	200	148	200	200	200
Starch	400	400	400	296	---	600	---
Lactose	---	---	---	---	600	---	---
Sodium bicarbonate	150	150	150	111	150	150	150
Microcrystalline cellulose	200	200	200	148	---	---	600
95% alcohol	Suitable volume	Suitable volume	Suitable volume	Suitable volume	Suitable volume	Suitable volume	Suitable volume
Talc powder	12	12	12	9	12	12	12
Foaming volume (ml)	>6	<6	>6	>6	>6	>6	>6
Others	Hygroscopicity and mucosity	Low and slow gas production	No hygroscopicity or mucosity	No hygroscopicity or mucosity	Hygroscopicity and mucosity	Poor compressibility	Rough plate surface

It can be seen from Table 1 that the use of citric acid easily absorbs moisture, the use of boric acid produce gas slowly, and the single use of starch, lactose, or microcrystalline cellulose results in defected tablets. Whereas the combined use of starch and microcrystalline cellulose can better solve problems like moisture absorption, mucosity, and surface smoothness. Therefore, the invention adopted formulae 3 and 4.

The invention has two formulae: formula (1), which is calculated based on the preparation of 1000 tablets

Azithromycin (calculated according to anhydrous azithromycin)	250.0g
Tartaric acid	200.0g
Sodium bicarbonate	150.0g
Starch	400.0g
Cellulose microcrystalline	200.0g
Talc powder	12.0g
	1212.0g

A suitable volume of 95% alcohol (500ml) is added during the preparation process as adhesives.

In the above-described formulae, azithromycin is the main gradient that plays a pharmacological role, while others are matrix ingredients in dosage form.

The invention also adopts formula (2):

Azithromycin (calculated according to anhydrous azithromycin)	500.0g
Tartaric acid	148.0g
Sodium bicarbonate	111.0g
Starch	296.0g
Cellulose microcrystalline	148.0g
Talc powder	9.0g
	1212.0g

A suitable volume of alcohol (500ml) is added during the preparation process as adhesives.

The final product contains 250mg or 500mg azithromycin per tablet when prepared according to the above prescription and routine preparation process of effervescent tablets.

Usage: 1~2 tablets, 1/d

The content of azithromycin, the effective component of the invention, is determined according to high-efficiency liquid-phase chromatography (Chinese Pharmacopoeia, 1995 Version, Volume 2, Appendix VD).

Azithromycin vaginal effervescent tablets can degrade after water absorption and gas production, and directly play a pharmacological role at localized sites at high concentration. With a strong broad-spectrum antibacterial role, the drug is particularly suitable for women with cervicitis, vaginitis, gonorrhoea, and complex infections. The effervescent tablet can avoid discomfort of the gastrointestinal tract like diarrhoea, abdominal pain, nausea, vomiting, and malabsorption caused by oral drugs, and is convenient for the patients to use with better curative effects.

Acute toxicity test: LD_{50} is 5564.0mg/kg (5139.7~6023.29mg/kg) when raw material of azithromycin is administrated via stomach lavage. And LD50 is 1144.87mg/kg (1034.16~1267.43mg/kg) and 983.2mg/kg (804.2~1116.89mg/kg) respectively when raw materials and vaginal effervescent tablets of azithromycin are administrated via intraperitoneal injection.

333.3mg/kg of azithromycin vaginal effervescent tablets administered at a time in the vagina of a rabbit is equivalent to 66.7 times of human volume, with no apparent toxic reaction.

After 15mg/kg of azithromycin vaginal effervescent tablets is administered at a time or continuously in the vagina of a rabbit, no sign of congestion, redness, or swelling is observed in the mucosa of the vagina.

The above experiments indicate that it is feasible to use azithromycin vaginal effervescent tablets in humans.

The example below is listed for further illustration.

<Example 1> According to the above described formula (1), material drugs (filtered with a 120-mesh sieve) and ingredients like tartaric acid, sodium bicarbonate, natrium, starch, and microcrystalline cellulose (filtered with a 100-mesh sieve) were weighed and mixed evenly. Soft material is prepared following the addition of 500ml alcohol, and then filtered with a 10-mesh sieve to make granules. The granules were baked and dried at 55~65°C, organized with a 10-mesh sieve, and then mixed evenly with talc powder. After the content and tablet weight calculation, the mixture was pressed into tablets weighing approx. 1.2g at ø15mm. ...

In the above example, sources and quality standards of raw material and ingredients are:

Azithromycin: Shijiazhuang First Pharmaceutical Plant. Meets the standards set by the Ministry of Health.

Tartaric acid: Beijing Chemical Plant. Meets the standards in the 1995 version of Chinese Pharmacopoeia.

Sodium bicarbonate: Tianjing Central Pharmaceutical Plant. Meets the standards in the 1995 version of Chinese Pharmacopoeia.

Starch: North China Pharmaceutical Plant. Meets the standards in the 1995 version of Chinese Pharmacopoeia.

Microcrystalline cellulose: Shandong Liaocheng Pharmaceutical Plant. Meets the standards in the 1995 version of Chinese Pharmacopoeia.

Alcohol: Beijing Chemical Reagent Plant. Meets the standards in the 1995 version of Chinese Pharmacopoeia.

Talc powder: Shanghai Plant of Drug-use Ingredients. Meets the standards in the 1995 version of Chinese Pharmacopoeia.

<Example 2> Raw material and ingredients were weighed according to formula 2. Others were the same as example 1.